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<p>(21) International Application Number: PCT/EP97/05986</p> <p>(22) International Filing Date: 23 October 1997 (23.10.97)</p> <p>(30) Priority Data: 9623522.1 11 November 1996 (11.11.96) GB</p> <p>(71) Applicant (for all designated States except US): PHARMACIA & UPJOHN S.P.A. [IT/IT]; Via Robert Koch, 1.2, I-20152 Milan (IT).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): COZZI, Paolo [IT/IT]; Via Zancilla, 48/5, I-20133 Milan (IT). BARALDI, Pier, Giovanni [IT/IT]; Via Tulipani, 73, I-44100 Ferrara (IT). BERIA, Italo [IT/IT]; Via G. Matteotti, 39, I-45030 Villamarzana (IT). CALDARELLI, Marina [IT/IT]; Via Besenzanica, 9, I-20147 Milan (IT). CAPOLONGO, Laura [IT/IT]; Via P. Rembrandt, 11, I-20147 Milan (IT). SPALLUTO, Giampiero [IT/IT]; Via Pomposa, 20, I-44100 Ferrara (IT). ROMAGNOLI, Romeo [IT/IT]; Via Bologna, 291, I-44100 Ferrara (IT).</p>		<p>(81) Designated States: AU, BG, BR, CA, CN, CZ, EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, SG, SI, TR, UA, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	
<p>(54) Title: BENZOHETEROCYCLIC DISTAMYCIN DERIVATIVES, PROCESS FOR PREPARING THEM, AND THEIR USE AS ANTITUMOR AND ANTIVIRAL AGENTS</p> <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div> <div style="text-align: center;"> <p style="text-align: right;">(II)</p> </div> <div style="text-align: center;"> <p style="text-align: right;">(III)</p> </div> <p>(57) Abstract</p> <p>Benzoheterocyclic distamycin derivatives of formula (I) wherein: n is 2, 3 or 4; A is O, S, or NR, wherein R is hydrogen or C₁–C₄ alkyl; B is CH or N; R₁ is hydrogen or C₁–C₄ alkyl; T is selected from: (i) formula (II) wherein: p is zero or 1; R₂ and R₃ are selected, each independently, from: hydrogen, C₁–C₄ alkyl optionally substituted by one or more fluorine atoms, and C₁–C₄ alkoxy; R₄ is C₁–C₄ alkyl or C₁–C₃ haloalkyl; X₁ is a halogen atom; and (ii) formula (III) wherein X₂ is a halogen atom; and pharmaceutically acceptable salts thereof, are described. Such compounds are useful as antineoplastic and antiviral agents.</p>			

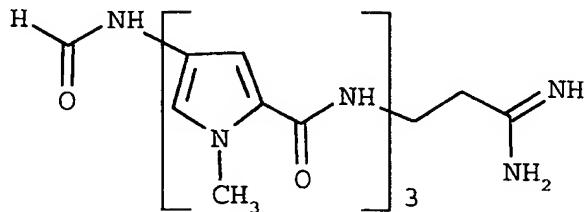
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BENZOHETEROCYCLIC DISTAMYCIN DERIVATIVES, PROCESS FOR PREPARING THEM, AND THEIR USE AS ANTITUMOR AND ANTIVIRAL AGENTS.

5 The present invention refers to new alkylating antitumor and antiviral agents related to the known antibiotic distamycin A:



which belongs to the family of the pyrroleamidine antibiotics and is reported to interact reversibly and selectively with DNA-AT sequences interfering with both replication and transcription [Nature, 203, 1064 (1964); FEBS Letters, 7 (1970) 90; Prog.Nucleic Acids Res.Mol.Biol., 15, 285 (1975)].

15 DE-A-1795539 describes the preparation of distamycin derivatives in which the formyl group of distamycin is replaced by hydrogen or by the acid residue of an organic C₁-C₄ aliphatic acid or of cyclopentylpropionic acid.

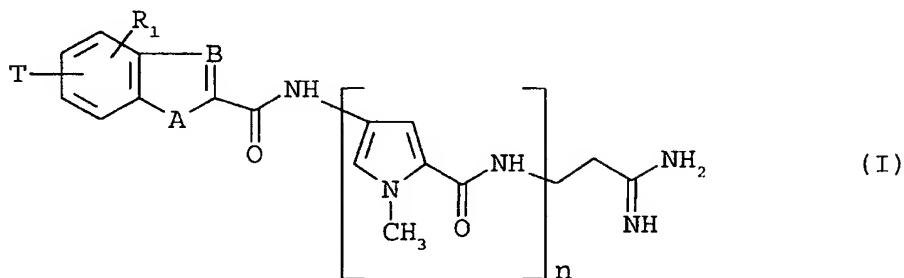
EP-B-246,868 describes distamycin analogues in which the 20 distamycin formyl group is substituted by aromatic, alicyclic or heterocyclic moieties bearing alkylating groups.

It has now been found that a new class of distamycin derivatives as defined hereinunder, wherein the distamycin 25 formyl group is substituted by a benzoheterocyclic ring bearing an alkylating group, shows valuable biological properties.

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Accordingly, the present invention relates to new distamycin derivatives of formula (I) as defined hereinunder, to a process for preparing them, to pharmaceutical compositions containing them and to their 5 use in therapy, particularly as antitumor and antiviral agents.

Therefore, object of the present invention are distamycin derivatives of formula:



10

wherein:

n is 2, 3 or 4;

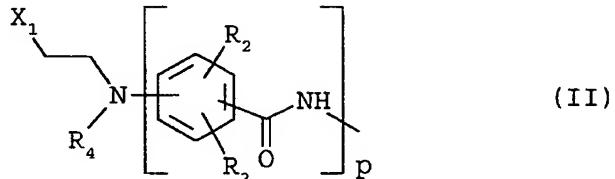
A is O, S or NR, wherein R is hydrogen or C₁-C₄ alkyl;

B is CH or N;

15 R₁ is hydrogen or C₁-C₄ alkyl;

T is selected from:

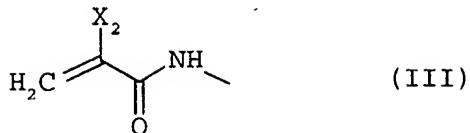
(i)



wherein:

20 p is zero or 1; R₂ and R₃ are selected, each independently, from: hydrogen, C₁-C₄ alkyl optionally substituted by one or more fluorine atoms, and C₁-C₄ alkoxy; R₄ is C₁-C₄ alkyl or C₁-C₃ haloalkyl; X₁ is a halogen atom; and

(ii)



wherein X_2 is a halogen atom;
or pharmaceutically acceptable salts thereof.

5

The present invention includes within its scope also all the possible isomers covered by formula (I) both separately and in admixture, as well as the metabolites and the pharmaceutically acceptable bio-precursors (otherwise known 10 as pro-drugs) of the compounds of formula (I).

The alkyl and alkoxy groups may have branched or straight chains. A C_1 - C_4 alkyl group is preferably methyl, ethyl or propyl, a C_1 - C_4 alkoxy group is preferably methoxy or 15 ethoxy, while a C_1 - C_3 haloalkyl group is preferably 2-chloroethyl or 2-bromoethyl. When substituted by one or more fluorine atoms, a C_1 - C_4 alkyl group is preferably a C_1 - C_4 perfluoroalkyl group, e.g. $-CF_3$. The halogen atoms X_1 and X_2 are preferably chlorine or bromine. Particularly 20 preferred values of n are 2 and 3.

When T is an alkylating moiety of formula (II) according to item (i) above with p equal to 1, the carboxamido group and the amino group on the phenyl ring are preferably in meta 25 or para position with respect to each other, while R_2 and R_3 can be in any of the free positions.

Pharmaceutically acceptable salts of the compounds of formula (I) are their salts with pharmaceutically 30 acceptable, either inorganic or organic, acids. Examples of

inorganic acids are hydrochloric, hydrobromic, sulfuric and nitric acid; examples of organic acids are acetic, propionic, succinic, malonic, citric, tartaric, methanesulfonic and p-toluenesulfonic acid.

5

A preferred class of distamycin derivatives according to the present invention is the one of formula (I) wherein:

n is 2 or 3;

A is O, S, NH or NCH₃;

10 B is CH or N;

R₁ is hydrogen;

T is a group of formula (II) according to item (i), wherein X₁ is chlorine or bromine; R₄ is ethyl, 2-chloroethyl or 2-bromoethyl; R₂ and R₃ are, each independently, hydrogen or 15 methyl; p is zero or 1; or

T is a group of formula (III) according to item (ii), wherein X₂ is bromine or chlorine.

Examples of specific compounds according to the present 20 invention, especially in the form of salts, preferably with hydrochloric acid, are the following:

1) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-chloroethyl)aminoindole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

25 2) 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-N,N-bis(2-chloroethyl)aminoindole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

30 3) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-chloroethyl)aminobenzofurane-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-

carboxamido] propionamidine;

4) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-chloroethyl)aminobenzimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

5) 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-N,N-bis(2-chloroethyl)aminobenzimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

10 6) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-chloroethyl)aminobenzothiophene-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

7) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-chloroethyl)aminobenzothiazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

15 8) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-bromoethyl)aminoindole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

20 9) 3-[1-methyl-4[1-methyl-4[1-methyl-5(α-bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

25 10) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α-bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

11) 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α-bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-

30

carboxamido]propionamidine;

12) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -bromoacrylamido)benzofurane-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

5 13) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -bromoacrylamido)benzothiophene-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

10 14) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -bromoacrylamido)benzothiazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

15 15) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -bromoacrylamido)benzimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

16) 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α -bromoacrylamido)benzimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

20 17) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -chloroacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

25 18) 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α -chloroacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

30 19) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -chloroacrylamido)benzimidazole-2-carboxamido]pyrrole-

2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

20) 3-[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-chloroethyl)
aminobenzene-1-carboxamido]indole-2-
5 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

21) 3-[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-chloroethyl)
aminobenzene-1-carboxamido]benzoimidazole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
10 carboxamido]propionamidine;

22) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

15 23) 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N,N-
bis(2-chloroethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

24) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
20 chloroethyl)aminobenzene-1-carboxamido]benzothiophene-
2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

25) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]benzofurane-2-
25 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

26) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]benzoimidazole-
2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
30 carboxamido]pyrrole-2-carboxamido]propionamidine;

27) 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N,N-
bis(2-chloroethyl)aminobenzene-1-

carboxamido]benzoimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

28) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
5 chloroethyl)aminobenzene-1-carboxamido]benzothiazole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

29) 3-[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-bromoethyl)
aminobenzene-1-carboxamido]indole-2-
10 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

30) 3-[1-methyl-4[1-methyl-4[1-methyl-5-[4-N,N-bis(2-
bromoethyl)aminobenzene-1-carboxamido]indole-2-
15 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

31) 3-[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-bromoethyl)
aminobenzene-1-carboxamido]benzoimidazole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

20 32) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
bromoethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

33) 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N,N-
25 bis(2-bromoethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

34) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
bromoethyl)aminobenzene-1-carboxamido]benzoimidazole-2-
30 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

35) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N-ethyl-N(2-

- 9 -

chloroethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

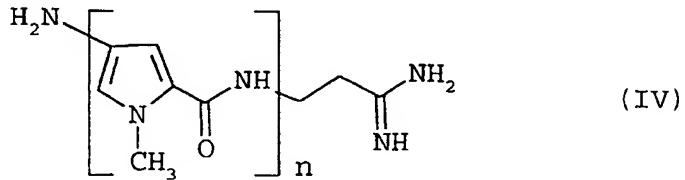
36) 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N-ethyl-N(2-
chloroethyl)aminobenzene-1-carboxamido]benzoimidazole-
2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

37) 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N-
ethyl-N(2-chloroethyl)aminobenzene-1-
carboxamido]indole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

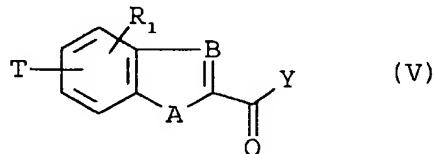
10 38) 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N-
ethyl-N(2-chloroethyl)aminobenzene-1-carboxamido]
15 benzoimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine.

Further object of the present invention is a process for
20 preparing the compounds of formula (I), and the
pharmaceutically acceptable salts thereof, which comprises:

(1) (a) reacting a compound of formula:



wherein n is 2, 3 or 4, with a compound of formula:



25

wherein:

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A is O, S or NR, wherein R is hydrogen or C₁-C₄ alkyl;

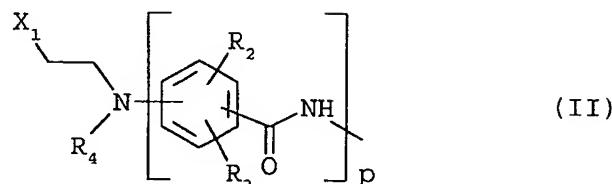
B is CH or N;

R₁ is hydrogen or C₁-C₄ alkyl;

T is selected from:

5

(i)

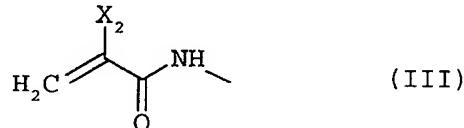


wherein:

10

p is zero or 1; R₂ and R₃ are selected, each independently, from: hydrogen, C₁-C₄ alkyl optionally substituted by one or more fluorine atoms, and C₁-C₄ alkoxy; R₄ is C₁-C₄ alkyl or C₁-C₃ haloalkyl; X₁ is a halogen atom; and

(ii)



15

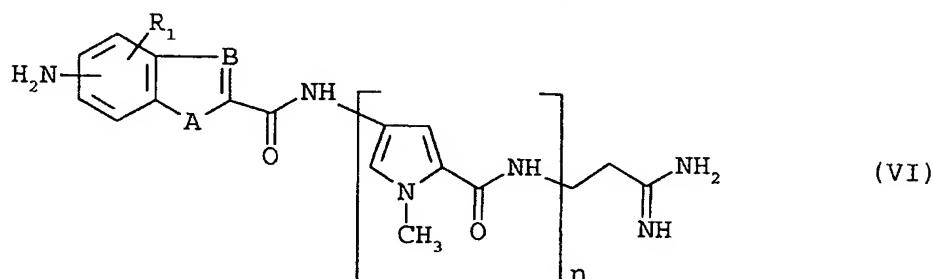
wherein X₂ is a halogen atom;

Y is hydroxy or a leaving group;

to obtain a compound of formula (I) as defined above;

or:

(b) reacting a compound of formula:

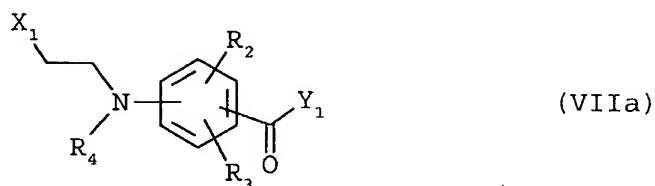


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wherein n, A, B, and R₁ are defined as above,

with a compound of formula:

- 11 -



wherein X_1 , R_2 , R_3 , and R_4 are defined as above, and Y_1 is hydroxy or a leaving group;
or with a compound of formula:



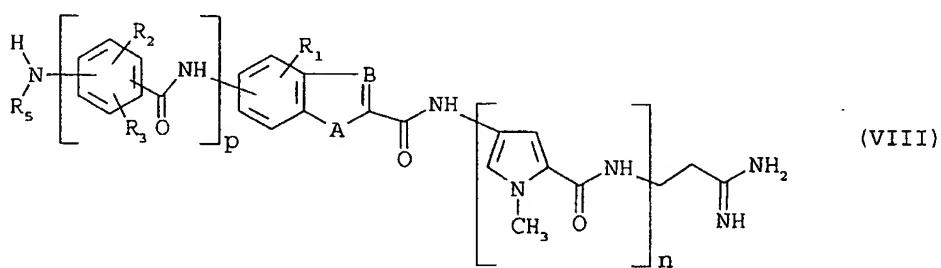
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wherein X_2 is as defined above, and Y_2 is hydroxy or a leaving group;

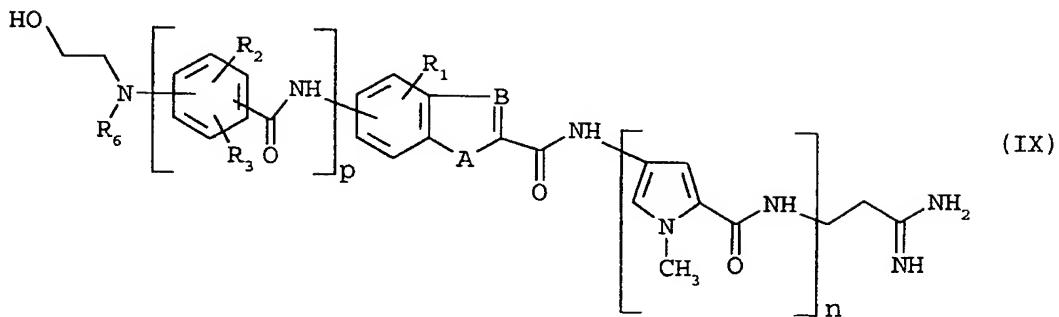
to obtain a compound of formula (I) as defined above,
wherein T is a group of formula (II) according to item
10 (i) with p equal to 1, or a group of formula (III)
according to item (ii);

or:

(c) reacting a compound of formula:



15 wherein p , n , A , B , R_1 , R_2 , and R_3 are defined as above,
and R_5 is hydrogen or C_1-C_4 alkyl,
with ethylene oxide, so obtaining a compound of
formula:



wherein p, n, A, B, R₁, R₂, and R₃ are defined as above, and R₆ is equal to R₅ when R₅ is C₁-C₄ alkyl, or R₆ is equal to -CH₂CH₂-OH when R₅ is hydrogen;

5 and then reacting the compound of formula (IX) with a halogenating agent, to obtain a compound of formula (I) as defined above, wherein T is a group of formula (II) according to item (i) with p equal to zero or 1;

and

10 (2) if necessary, converting the so obtained compound of formula (I) into a pharmaceutically acceptable salt thereof.

15 The reaction of a compound of formula (IV) with a compound of formula (V) (process (a)) can be carried out according to known methods, for instance those described in EP-B-246,868.

20 The reaction between a compound of formula (IV) and a compound of formula (V) wherein Y is hydroxy, is preferably carried out with a molar ratio (IV):(V) of from 1:1 to 1:2, in an organic solvent, such as, e.g., dimethylsulphoxide, dimethylacetamide, dimethylformamide, ethanol, benzene, or pyridine, in the presence of an organic or inorganic base such as, e.g., triethylamine, N,N'-diisopropylethylamine, 25 or sodium or potassium carbonate or bicarbonate, and a condensing agent such as, e.g., N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, N,N'-dicyclohexylcarbodiimide, or

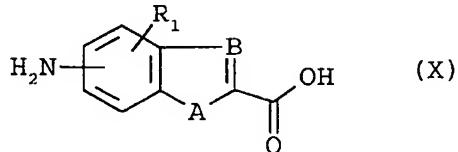
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1-hydroxybenzotriazole hydrate. The reaction temperature may vary from about -10°C to about 100°C, and the reaction time from about 1 to about 24 hours.

5 The reaction between a compound of formula (IV) and a compound of formula (V), wherein Y is a leaving group as defined above, may be carried out with a molar ratio (IV):(V) of from about 1:1 to about 1:2, in an organic solvent, such as, e.g., dimethylformamide, dioxane, 10 pyridine, tetrahydrofuran, or mixtures thereof with water, optionally in the presence of an organic base, e.g. N,N'-diisopropylethylamine, triethylamine, or an inorganic base, e.g. sodium or potassium bicarbonate, at a temperature of from about 0°C to about 100°C, and for a time varying from 15 about 2 hours to about 48 hours.

The compounds of formula (IV) are known compounds, or may be prepared by known methods from known compounds: see, for instance, Arcamone et al. Gazzetta Chim. Ital. 97, 1097 20 (1967).

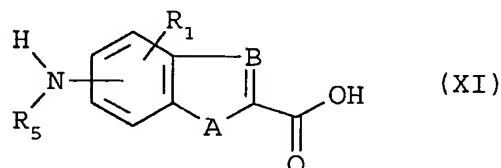
The compounds of formula (V), wherein Y is hydroxy, and T is a group of formula (II) according to item (i) with p equal to 1, or a group of formula (III) according to item 25 (ii), can be prepared by reacting an amino compound of formula:



wherein A, B and R₁ are as defined above, with a carboxylic acid, or a derivative thereof, of formula (VIIa) or (VIIb)

as defined above.

The compounds of formula (V), wherein Y is hydroxy, and T is a group of formula (II) according to item (i) with p 5 equal to zero, can be prepared by reacting a compound of formula:



wherein A, B, R₁, and R₅ are defined as above, with ethylene oxide and then with a halogenating agent, analogously to 10 what described above for process (c). Before carrying out the reaction, the carboxyl group is preferably protected with a suitable protecting group according to known techniques.

15 The compounds of formula (V) wherein Y is a leaving group can be prepared starting from the corresponding acids through well known reactions.

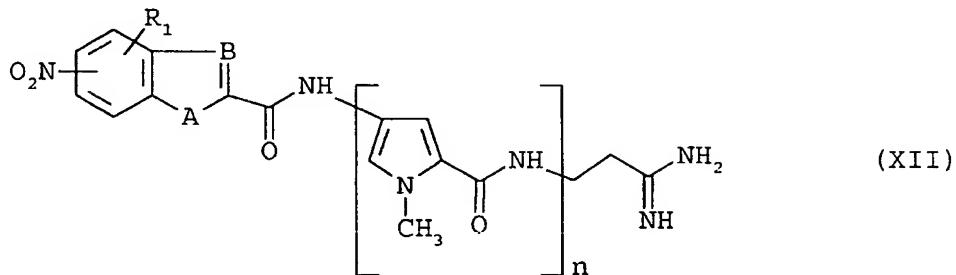
The carboxylic acids of formulas (VIIa) and (VIIb), or the 20 derivatives thereof, are commercially available products, or may be prepared through reactions well known in organic chemistry (see e.g. Tetrahedron Letters 31 1299 (1990), Anti-cancer Drug Design 9, 511 (1994)), JACS 62 3495 (1940), J.Org.Chem. 26 4996-97 (1961), or Synth.Commun. 24 25 3129-3134 (1994)).

The compounds of formulas (X) and (XI) are commercial products, or can be obtained by known methods (see e.g. J.Am.Chem.Soc. 80, 4621 (1958), Helv.Chim.Acta 31, 75

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(1948), *Synth.Commun.* 21, 959 (1991), *Anti-cancer Drug Design* 10, 25 (1995), *J.Org.Chem.* 26, 4996-97 (1961), or *Synth.Commun.* 24, 3129-3134 (1994)).

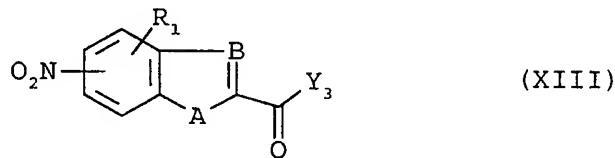
5 The compounds of formula (VI) can be obtained by nitro-group reduction, according to known methods, of compounds of formula:



wherein n, A, B and R₁ are as defined above.

10

The nitro-derivatives of formula (XII) can be obtained, in turn, by reacting a compound of formula (IV) as defined above with a compound of formula:



15 wherein A, B and R₁ are as defined above, and Y₃ is hydroxy or a leaving group. The compounds of formula (XIII) are known compounds, or may be obtained by known methods (see, e.g., *Tetrahedron Letters* 31, 1299 (1990), *Anti-cancer Drug Design* 9, 511 (1994)), *JACS* 62, 3495 (1940), *J.Org.Chem.* 26, 4996-97 (1963), or *Synth.Commun.* 24, 3129-3134 (1994)).

20 The reaction according to process (c) can be carried out analogously to what described in U.S. Patent No. 4,738,980. The halogenating agent may be, e.g., an elemental halide, such as chlorine or bromine, or a thionyl halide, such as

thionylchloride. The starting compounds of formula (VIII) may be obtained according to known reactions, e.g. by mono-alkylation of the amino-compounds of formula (VI) as defined above, optionally previously condensed with the 5 corresponding amino benzoic acid, or a derivative thereof.

In the above formulas, the groups Y , Y_1 , Y_2 , and Y_3 are hydroxy or leaving groups selected, for instance, from chloro, 2,4,5-trichlorophenoxy, 2,4-dinitro-phenoxy, 10 succinimido-N-oxy, imidazolyl, and the like.

Salification of a compound of formula (I), as well as preparation of a free compound starting from a salt, may be carried out by known standard methods. Well known 15 procedures such as, e.g., fractional crystallization or chromatography, may also be followed for separating a mixture of isomers of formula (I) into the single isomers.

The compounds of formula (I) may be purified by 20 conventional techniques such as, e.g., silica gel or alumina column chromatography, and/or by recrystallization from an organic solvent such as, e.g., a lower aliphatic alcohol, e.g. methyl, ethyl or isopropyl alcohol, or dimethylformamide.

25

PHARMACOLOGY

The compounds of formula (I) according to the present invention are useful as antineoplastic and antiviral agents. Particularly, they show cytostatic properties 30 towards tumor cells, so that they can be useful to inhibit growth of various tumors in mammals, including humans, such as, for instance, carcinomas, e.g. mammary carcinoma, lung

carcinoma, bladder carcinoma, colon carcinoma, ovary and endometrial tumors. Other neoplasias in which the compounds of the present invention can find application are, for instance, sarcomas, e.g. soft tissue and bone sarcomas, and 5 the hematological malignancies such as, e.g. leukemias.

The in vitro antitumor activity was evaluated by cytotoxicity studies carried out on murine L₁₂₁₀ leukemia cells. Cells were derived from in vivo tumors and 10 established in cell culture. Cells were used until the tenth passage. Cytotoxicity was determined by counting surviving cells after 48 hours treatment.

The percentage of cell growth in the treated cultures was compared with that of controls. IC₅₀ values (concentration 15 inhibiting 50% of the cellular growth in respect to controls) were calculated on dose-response.

The compounds of the invention were tested also in vivo on L₁₂₁₀ murine leukemia and on murine reticulosarcoma M 5076, 20 showing a very good antitumoral activity, with the following procedure.

L₁₂₁₀ murine leukemia was maintained in vivo by i.v. serial transplantation. For experiments, 10⁵ cells were injected i.p. in CD2F1 female mice, obtained from Charles River Italy. 25 Animals were 8 to 10 weeks old at the beginning of the experiments. Compounds were administered i.v. at day +1 after tumor cells injections.

M5076 reticulosarcoma was maintained in vivo by i.m. serial transplantation. For experiments, 5x10⁵ cells were injected 30 i.m. in C57B16 female mice, obtained from Charles River Italy. Animals were 8 to 10 weeks old at the beginning of the experiments. Compounds were administered i.v. at day 3, 7 and

11 after tumor injection.

Survival time of mice and tumor growth were calculated and activity was expressed in terms of T/C% and T.I.%.

5 median survival time treated group
 T/C = $\frac{\text{median survival time treated group}}{\text{median survival time untreated group}} \times 100$

T.I. = % inhibition of tumor growth respect to control

10 Tox = number of mice which died for toxicity.

Tox determination was made when mice died before the control and/or tested significant body weight loss and/or spleen and/or liver size reduction were observed.

15 The compounds of the invention show also a remarkable effectiveness in interfering with the reproductive activity of pathogenic viruses and protect tissue cells from viral infections. For example, they show activity against DNA viruses such as, for instance, herpes, e.g. herpes simplex and herpes zoster viruses, virus vaccinia, RNA viruses such as, e.g., Rhinovirus and Adenovirus, and against retroviruses such as, for instance, sarcoma viruses, e.g., murine sarcoma virus, and leukemia viruses, e.g. Friend leukemia virus.

25

For example, effectiveness against herpes, coxsackie and respiratory syncytial viruses was tested in a fluid medium as follows. Serial two-fold dilutions of the compounds from 200 to 1.5 mcg/ml were distributed in duplicate 0.1 ml/well in 96 well microplates for tissue culture. Cell suspensions (2×10^5 cells/ml) infected with about 5×10^{-3} TCID₅₀ of virus/cell were immediately added 0.1 ml/well.

After 3-5 day incubation at 37°C in CO₂ 5%, the cell

cultures were evaluated by microscope observation and Minimum Inhibiting Concentration (MIC) was determined, MIC being the minimum concentration which determines a reduction of cytopathic effect in comparison with the 5 infected controls.

The compounds of the invention can be administered to mammals, including humans, through the usual routes, for example, parenterally, e.g. by intravenous injection or 10 infusion, intramuscularly, subcutaneously, topically or orally. The dosage depends on the age, weight and conditions of the patient and on the administration route. For example, a suitable dosage for administration to adult humans may range from about 0.1 to about 150-200 mg pro 15 dose 1-4 times a day.

Further object of the present invention are pharmaceutical compositions, which comprise a compound of formula (I) as an active principle, in association with one or more 20 pharmaceutically acceptable carrier and/or diluent.

The pharmaceutical compositions of the present invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form. For 25 instance, solutions for intravenous injection or infusion may contain as a carrier, for example, sterile water or preferably, they may be in the form of sterile aqueous isotonic saline solutions.

Suspensions or solutions for intramuscular injections may 30 contain, together with the active compound a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol,

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and if desired, a suitable amount of lidocaine hydrochloride.

In the forms for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active 5 ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g., lactose, dextrose, saccharose, cellulose, corn starch and 10 potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl cellulose, polyvinyl-pyrrolidone; disaggregating agents, e.g. starch, alginic 15 acid, alginates, sodium starch glycolate; effervescent mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulation. Said 20 pharmaceutical preparation may be manufactured by known techniques, for example by means of mixing, granulating, tabletting, sugar-coating or film-coating processes.

Further object of the present invention are compounds of 25 formula (I) for use in a method for treating the human or animal body by therapy.

Furthermore, the present invention provides a method for treating tumors and viral infections in a patient in need of it, which comprises administering to said patient a 30 composition of the invention.

A further object of the present invention is a combined method for treating cancer or for ameliorating the

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conditions of mammals, including humans, suffering from cancer, said method comprising administering a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an additional antitumor agent, close enough in time and 5 in amounts sufficient to produce a therapeutically useful effect.

The present invention also provides products containing a compound of formula (I), or a pharmaceutically acceptable 10 salt thereof, and an additional antitumour agent as a combined preparation for simultaneous, separate or sequential use in anti-cancer therapy.

The term "antitumor agent" is meant to comprise both a single antitumor drug and "cocktails" i.e. a mixture of 15 such drugs, according to the clinical practice. Examples of antitumor agents that can be formulated with a compound of formula (I), or alternatively, can be administered in a combined method of treatment, include doxorubicin, daunomycin, epirubicin, idarubicin, etoposide, fluoro-20 uracil, melphalan, cyclophosphamide, 4-demethoxy daunorubicin, bleomycin, vinblastin, and mitomycin, or mixtures thereof.

The following examples are given to better illustrate the 25 invention, but do not limit the scope of the invention itself.

Example 1

30 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-chloroethyl)aminoindole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-

carboxamido]propionamidine hydrochloride**Step I: The intermediate 5-N,N-bis(2-chloroethyl)aminoindole-2-carboxylic acid**

5 To a solution of 200 mg of ethyl 5-aminoindole-2-carboxylate (prepared as reported in J.Am.Chem.Soc. 80, 4621 (1958)) in 10 ml of methanol cooled at -10°C, cold ethylene oxide (2.5 ml) was added. The reaction flask was sealed and allowed to reach room temperature overnight.

10 Methanol and excess of ethylene oxide were removed by evaporation and the crude residue purified by flash chromatography obtaining 230 mg of ethyl 5-N,N-bis(2-hydroxyethyl)aminoindole-2-carboxylate which was cooled in ice and 2 ml of phosphorus oxychloride were added. The

15 solution was heated at 100°C for one hour, then solvent evaporated under vacuum, the residue dissolved in 7 ml of 23% hydrochloric acid and heated at 100°C for two hours. The solution was cooled at room temperature, diluted with 30 ml of water and extracted twice with ethyl acetate (2x50

20 ml). The organic phases were evaporated in vacuo and the residue purified by flash chromatography using a methylene chloride/methanol mixture, yielding 220 mg of the intermediate.

25 By analogous procedure and using the opportune starting materials the following products can be obtained:
5-N,N-bis(2-chloroethyl)aminobenzofurane-2-carboxylic acid;
1-methyl-5-N,N-bis(2-chloroethyl)aminoindole-2-carboxylic acid;
30 5-N,N-bis(2-chloroethyl)aminobenzothiophene-2-carboxylic acid
5-N,N-bis(2-chloroethyl)aminobenzimidazole-2-carboxylic

acid;

1-methyl-5-N,N-bis(2-chloroethyl)aminobenzoimidazole-2-carboxylic acid;

5-N,N-bis(2-chloroethyl)aminobenzothiazole-2-carboxylic acid;

5 acid;

5-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]indole-2-carboxylic acid;

5-[4-[N-ethyl-N(2-chloroethyl)]aminobenzene-1-carboxamido]indole-2-carboxylic acid;

10 5-N,N-bis(2-bromoethyl)aminoindole-2-carboxylic acid;

5-[4-N,N-bis(2-bromoethyl)aminobenzene-1-carboxamido]indole-2-carboxylic acid.

Step II: The title compound

15 A solution of 263 mg of N-deformyldistamycin A dihydrochloride (prepared as reported in J.Med.Chem. 32, 774-778 (1989)) in 5 ml of dry dimethylformamide (DMF) was cooled to 5°C and added with 86 ml of N,N'-diisopropylethylamine. After 10 min, 175 mg of intermediate obtained from step I and 192 mg of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDCI) were added. The reaction was stirred at room temperature for 10 hours, then 2N hydrochloric acid was added up to pH=4. The solvent was removed under reduced pressure and the crude residue purified by flash chromatography (methylene chloride/methanol:8/2) to give 210 mg of the title compound as a yellow solid.

FAB-MS: m/z 736, (20, [M+H]⁺)

PMR (DMSO-d₆) δ :

30 11.35 (d, J=1.8 Hz, 1H), 10.29 (s, 1H), 9.96 (s, 1H), 9.89 (s, 1H), 8.93 (b.s., 2H), 8.56 (b.s., 2H), 8.18 (t, J=5.6 Hz, 1H), 7.30 (m, 2H), 7.10 (d, J=1.8 Hz, 1H), 7.20 (d,

J=1.8 Hz, 1H), 7.14 (d, J=1.8 Hz, 1H), 7.04 (d, J=1.8 Hz, 1H) 7.02 (d, J=1.8 Hz, 1H), 6.92 (d, J=1.8 Hz, 1H), 6.91 (d, J=1.8 Hz, 1H), 6.84 (dd, J=2.3 Hz and J=9.0 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.66 (m, 8H),
5 3.46 (m, 2H), 2.57 (m, 2H).

By analogous procedure and using the opportune starting materials the following products can be obtained:

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-N,N-bis(2-chloroethyl)aminoindole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

FAB-MS: m/z 750, (25, [M+H]⁺)

PMR (DMSO-d₆) δ :

15 10.35 (s, 1H), 9.99 (s, 1H), 9.92 (s, 1H), 8.97 (b.s., 2H), 8.60 (b.s., 2H), 8.22 (t, J=5.5 Hz, 1H), 7.43 (d, J=9.8 Hz, 1H), 6.9-7.4 (m, 9H), 3.96 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.72 (m, 8H), 3.50 (m, 2H), 2.61 (m, 2H);

20

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-chloroethyl)aminobenzofurane-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

25 FAB-MS: m/z 737, (20, [M+H]⁺)

PMR (DMSO-d₆) δ:

10.60 (s, 1H), 9.98 (s, 1H), 9.90 (s, 1H), 8.94 (b.s., 2H), 8.56 (b.s., 2H), 8.19 (t, J=5.6 Hz, 1H), 7.52 (d, J=9.0 Hz, 1H), 7.50 (s, 1H), 6.9-7.4 (m, 8H), 3.86 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.75 (m, 8H), 3.50 (m, 2H), 2.61 (m, 2H);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-chloroethyl)aminobenzimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

5 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-N,N-bis(2-chloroethyl)aminobenzimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

10 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-chloroethyl)aminobenzothiophene-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

FAB-MS: m/z 753, (60, [M+H]⁺)

15 PMR (DMSO-d₆) δ:

10.55 (s, 1H), 9.97 (s, 1H), 9.89 (s, 1H), 8.17 (t, J=5.9 Hz, 1H), 8.06 (s, 1H), 7.81 (d, J=9.0 Hz, 1H), 7.29 (d, J=1.7 Hz, 1H), 7.23 (d, J=1.7 Hz, 1H), 7.21 (d, J=2.6 Hz, 1H), 7.16 (d, J=1.7 Hz, 1H), 7.09 (d, J=1.7 Hz, 1H), 7.06 (d, J=1.7 Hz, 1H), 7.06 (dd, J=9.0, 2.6 Hz, 1H), 6.95 (d, J=1.7 Hz, 1H), 3.7-3.9 (m, 8H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.48 (m, 2H), 2.58 (t, J=6.6 Hz, 2H);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-

25 chloroethyl)aminobenzothiazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-N,N-bis(2-bromoethyl)aminoindole-2-carboxamido]pyrrole-2-

30 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [1-methyl-5- [4-N,N-
bis (2-chloroethyl) aminobenzene-1-carboxamido] indole-2-
carboxamido] pyrrole-2-carboxamido] pyrrole-2-
carboxamido] pyrrole-2-carboxamido] propionamidine
5 hydrochloride;

3- [1-methyl-4 [1-methyl-4 [5- [4-N,N-bis (2-
bromoethyl) aminobenzene-1-carboxamido] indole-2-
carboxamido] pyrrole-2-carboxamido] pyrrole-2-
carboxamido] propionamidine hydrochloride;

10 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5- [4-N,N-bis (2-
bromoethyl) aminobenzene-1-carboxamido] indole-2-
carboxamido] pyrrole-2-carboxamido] pyrrole-2-
carboxamido] propionamidine hydrochloride;

15 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5- [4-N-ethyl-N (2-
chloroethyl) aminobenzene-1-carboxamido] indole-2-
carboxamido] pyrrole-2-carboxamido] pyrrole-2-
carboxamido] propionamidine hydrochloride;

20 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
bromoacrylamido) benzimidazole-2-carboxamido] pyrrole-2-
carboxamido] pyrrole-2-carboxamido] pyrrole-2-
carboxamido] propionamidine hydrochloride.

25 Example 2

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
bromoacrylamido) benzofuran-2-carboxamido] pyrrole-2-
carboxamido] pyrrole-2-carboxamido] pyrrole-2-
30 carboxamido] propionamidine hydrochloride

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Step I: The intermediate 5- α -bromoacrylamidobenzofurane-2-carboxylic acid

To a solution of 500 mg of commercial α -bromoacrylic acid in 5 ml of acetonitrile, a solution of 343 mg of N,N-dicyclohexylcarbodiimide in 15 ml of acetonitrile was slowly added. After one hour, the solution obtained after filtration of the precipitate was added to a solution of 294 mg of 5-amino-2-benzofuranic acid (prepared as reported in *Helv.Chim.Acta* 31, 75 (1948)) and 229 mg of sodium bicarbonate in 20 ml of water. The reaction was stirred at room temperature for one hour, then 2N hydrochloric acid was added up to pH=4. The solution was extracted with ethyl acetate (3x10 ml), dried over sodium sulfate and evaporated to dryness in vacuo and the crude residue purified by flash chromatography with a methylene chloride/methanol mixture to yield 500 mg of the intermediate as a pale yellow solid.

By analogous procedure and using the opportune starting materials the following products can be obtained:

20 5- α -bromoacrylamidobenzothiophene-2-carboxylic acid;
5- α -bromoacrylamidoindole-2-carboxylic acid;
1-methyl-5- α -bromoacrylamidoindole-2-carboxylic acid;
5- α -bromoacrylamidobenzimidazole-2-carboxylic acid;
1-methyl-5- α -bromoacrylamidobenzimidazole-2-carboxylic
25 acid;
5- α -bromoacrylamidobenzothiazole-2-carboxylic acid;
5- α -chloroacrylamidoindole-2-carboxylic acid;
1-methyl-5- α -chloroacrylamidoindole-2-carboxylic acid;
5- α -chloroacrylamidobenzimidazole-2-carboxylic acid.

Step II: The title compound

A solution of 263 mg of N-deformyldistamycin A dihydrochloride (prepared as reported in J.Med.Chem. 32, 774-778 (1989).) in 5 ml of dry DMF was cooled to 5°C and 5 added with 0.086 ml of N,N'-diisopropylethylamine. After 10 min, 180 mg of the intermediate obtained from step I, and 192 mg of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDCI) were added. The reaction was stirred at room 10 temperature for 16 hours, then 2N hydrochloric acid was added up to pH=4. The solvent was evaporated in vacuo and 15 the crude residue purified by flash chromatography (methylene chloride/methanol:8/2) to yield a yellow oil which was precipitated from methanol/diethyl ether obtaining 240 mg of the title compound as a pale yellow solid.

FAB-MS: m/z 746, (25, $[M+H]^+$)

U.V. (EtOH 95%) $\lambda_{max} = 315.4$, $\epsilon = 42622$

PMR (DMSO-d₆) δ :

10.69 (s, 1H), 10.39 (s, 1H), 10.00 (s, 1H), 9.90 (s, 1H),
20 8.92 (b.s., 2H), 8.52 (b.s., 2H), 8.2 (m, 2H), 7.66 (m,
3H), 7.32 (d, J=1.8 Hz, 1H), 7.24 (d, J=1.8 Hz, 1H), 7.17
(d, J=1.8 Hz, 1H), 7.15 (d, J=1.8 Hz, 1H) 7.07 (d, J=1.8
Hz, 1H), 6.96 (d, J=1.8 Hz, 1H), 6.77 (d, J=3.1 Hz, 1H),
6.31 (d, J=3.1 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80
25 (s, 3H), 3.51 (m, 2H), 2.60 (m, 2H).

By analogous procedure and using the opportune starting materials the following products can be obtained:

30 3-[1-methyl-4[1-methyl-4[1-methyl-5(α -bromoacrylamido)indole-2-carboxamido]pyrrole-2-

-29-

carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

FAB-MS: m/z 269, (10, [M+H]⁺)

U.V. (EtOH 95%) $\lambda_{\text{max}} = 310$, $\epsilon = 35011$

5 PMR (DMSO-d₆) δ :

10.39 (s, 1H), 10.18 (s, 1H), 9.93 (s, 1H), 8.92 (b.s., 2H), 8.54 (b.s., 2H), 8.19 (t, J=5.7 Hz, 1H), 8.01 (d, J=1.5 Hz, 1H), 7.50 (d, J=9.0 Hz, 1H), 7.42 (dd, J=9.0 Hz and J=1.5 Hz, 1H), 7.29 (d, J=1.8 Hz, 1H), 7.16 (s, 1H), 10 7.15 (d, J=1.8 Hz, 1H) 7.06 (d, J=1.8 Hz, 1H), 6.92 (d, J=1.8 Hz, 1H), 6.72 (d, J=3.1 Hz, 1H), 6.25 (d, J=3.1 Hz, 1H), 3.97 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.44 (m, 2H), 2.60 (m, 2H);

15 3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

FAB-MS: m/z 744, (100, [M+H]⁺)

20 U.V. (EtOH 95%) $\lambda_{\text{max}} = 500$, $\epsilon = 39053$

PMR (DMSO-d₆) δ :

11.70 (d, J=1.7 Hz, 1H), 10.42 (s, 1H), 10.15 (s, 1H), 9.99 (s, 1H), 9.90 (s, 1H), 8.98 (b.s., 2H), 8.67 (b.s., 2H), 8.20 (t, J=5.7 Hz, 1H), 7.95 (d, J=2.1 Hz, 1H), 7.36 (m, 2H), 7.26 (d, J=1.8 Hz, 1H), 7.24 (s, 1H), 7.22 (d, J=1.8 Hz, 1H), 7.16 (d, J=1.8 Hz, 1H) 7.06 (d, J=1.8 Hz, 1H), 7.03 (d, J=1.8 Hz, 1H), 6.91 (d, J=1.8 Hz, 1H), 6.72 (d, J=3.0 Hz, 1H), 6.23 (d, J=3.0 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.46 (m, 2H), 2.59 (m, 2H);

30

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5(α -

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bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

FAB-MS: m/z 760, (100, [M+H]⁺)

5 PMR (DMSO-d₆) δ :

10.44 (s, 1H), 10.23 (s, 1H), 10.00 (s, 1H), 9.93 (s, 1H),
8.97 (b.s., 2H), 8.60 (b.s., 2H), 8.22 (t, J=5.7 Hz, 1H),
8.05 (d, J=1.8 Hz, 1H), 7.54 (d, J=8.9 Hz, 1H), 7.47 (dd,
J=8.9 Hz and J=1.9 Hz, 1H), 7.25 (d, J=1.8 Hz, 1H), 7.21
10 (s, 1H), 7.19 (d, J=1.8 Hz, 1H), 7.12 (d, J=1.8 Hz, 1H),
7.07 (d, J=1.8 Hz, 1H), 7.05 (d, J=1.8 Hz, 1H), 6.95 (d,
J=1.8 Hz, 1H), 6.77 (d, J=3.1 Hz, 1H), 6.29 (d, J=3.1 Hz,
1H), 4.01 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H),
3.50 (m, 2H), 2.61 (m, 2H);

15

3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α-bromoacrylamido)benzothiophene-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

20 FAB-MS: m/z 760, (20, [M+H]⁺)

PMR (DMSO-d₆) δ :

10.71 (s, 1H), 10.48 (s, 1H), 9.99 (s, 1H), 9.90 (s, 1H),
8.96 (b.s., 2H), 8.65 (b.s., 2H), 8.32 (d, J=2.1 Hz, 1H),
8.24 (s, 1H), 8.19 (t, J=5.6 Hz, 1H), 7.95 (d, J=9.0 Hz,
1H), 7.65 (dd, J=2.1 Hz and J=9.0 Hz, 1H), 7.29 (d, J=1.8
Hz, 1H), 7.22 (d, J=1.8 Hz, 1H), 7.16 (d, J=1.8 Hz, 1H),
7.09 (d, J=1.8 Hz, 1H), 7.03 (d, J=1.8 Hz, 1H), 6.91 (d,
J=1.8 Hz, 1H), 6.80 (d, J=3.0 Hz, 1H), 6.31 (d, J=3.0 Hz,
1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.46 (m,
30 2H), 2.58 (m, 2H);

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
bromoacrylamido)benzothiazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;

5 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
bromoacrylamido)benzimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [1-methyl-5 (α -
10 bromoacrylamido)benzimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
15 chloroacrylamido)indole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [1-methyl-5 (α -
chloroacrylamido)indole-2-carboxamido]pyrrole-2-
20 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
chloroacrylamido)benzimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride.

25

Example 3

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [1-methyl-5 - [4-N,N-
30 bis(2-chloroethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine

hydrochloride**Step I: The intermediate 1-methyl-5-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]indole-2-carboxylic acid**

5 To a solution of 495 mg of 4-N,N-bis(2-chloroethyl)aminobenzoic acid (prepared as reported in Example 1, Step I) in 20 ml of benzene, 1 ml of thionyl chloride was added. The mixture was refluxed for two hours, 10 the solvent evaporated under vacuum, the crude solid residue dissolved in 15 ml of dioxane and added portionwise to a solution of 167 mg of 1-methyl-5-aminoindole-2-carboxylic acid (prepared as reported in J.Am.Chem.Soc. 80, 4621 (1958)) and 239 mg of sodium bicarbonate in 20 ml of 15 water.

The mixture was stirred for one hour and then added with 2N hydrochloric acid up to pH=4. The solvent was evaporated in vacuo and the residue purified by flash chromatography on silica gel with a methylene chloride/methanol mixture, 20 yielding 400 mg of the intermediate.

By analogous procedure and using the opportune starting materials the following products can be obtained:

25 5-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]indole-2-carboxylic acid;

5-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]benzofuran-2-carboxylic acid;

5-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]benzothiophene-2-carboxylic acid;

30 5-[4-N,N-bis(2-chloroethyl)aminobenzene-1-carboxamido]benzimidazole-2-carboxylic acid;

1-methyl-5-[4-N,N-bis(2-chloroethyl)aminobenzene-1-

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carboxamido]benzimidazole-2-carboxylic acid;
5-[4-N,N-bis(2-chloroethyl)aminobenzene-1-
carboxamido]benzothiazole-2-carboxylic acid;
5-[4-N,N-bis(2-bromoethyl)aminobenzene-1-
5 carboxamido]indole-2-carboxylic acid;
1-methyl-5-[4-N,N-bis(2-bromoethyl)aminobenzene-1-
carboxamido]indole-2-carboxylic acid;
5-[4-N,N-bis(2-bromoethyl)aminobenzene-1-
carboxamido]benzimidazole-2-carboxylic acid;
10 5-[4-[N-ethyl-N-(2-chloroethyl)]aminobenzene-1-
carboxamido]indole-2-carboxylic acid;
1-methyl-5-[4-N,N-bis(2-chloroethyl)aminobenzene-1-
carboxamido]indole-2-carboxylic acid;
5-[4-N,N-bis(2-chloroethyl)aminobenzene-1-
15 carboxamido]benzimidazole-2-carboxylic acid;
1-methyl-5-[4-N,N-bis(2-chloroethyl)aminobenzene-1-
carboxamido]benzimidazole-2-carboxylic acid.

Step II: The title compound

20 To a solution of 320 mg of intermediate (prepared as reported in Step I) in 10 ml of benzene, 0.5 ml of thionyl chloride were added. The mixture was refluxed for two hours, the solvent evaporated under vacuum, the crude solid residue dissolved in 15 ml of dioxane and added portionwise
25 to a solution of 200 mg of N-deformyldistamycin A dihydrochloride (prepared as reported in J.Med.Chem. 32, 774-778 (1989)), 95 mg of sodium bicarbonate in 10 ml of water.

The mixture was stirred for one hour and then added of 2N
30 hydrochloric acid up to pH=4. The solvent was evaporated in vacuo and the residue purified by flash chromatography (methylene chloride/methanol:8/2) to yield 250 mg of the

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title compound as a pale yellow solid.

FAB-MS: m/z 869, (40, [M+H]⁺)

PMR (DMSO-d₆) δ :

10.39 (s, 1H), 9.98 (s, 1H), 9.91 (s, 1H), 9.88 (s, 1H),
5 8.97 (b.s., 2H), 8.63 (b.s., 2H), 8.20 (t, J=5.6 Hz, 1H),
8.15 (d, J=1.8 Hz, 1H), 7.90 (m, 2H), 7.58 (dd, J=9.0 Hz
and J=1.8 Hz, 1H), 7.50 (d, J=9.0 Hz, 1H), 7.33 (d, J=1.8
Hz, 1H), 7.24 (d, J=1.8 Hz, 1H), 7.21 (s, 1H), 7.19 (d,
J=1.8 Hz, 1H), 7.18 (d, J=1.8 Hz, 1H), 7.12 (d, J=1.8 Hz,
10 1H), 7.07 (d, J=1.8 Hz, 1H), 6.95 (d, J=1.8 Hz, 1H), 6.84
(m, 2H), 4.01 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.80 (s,
3H), 3.78 (m, 8H), 3.50 (m, 2H), 2.61 (m, 2H).

By analogous procedure and using the opportune starting
15 materials the following products can be obtained:

3-[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;

20 3-[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]benzoimidazole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;

25 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine
hydrochloride;

30 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]benzothiophene-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine

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hydrochloride;

FAB-MS: m/z 871, (20, [M+H]⁺)

U.V. (EtOH 95%) $\lambda_{\text{max}} = 313.8$, $\epsilon = 48830$

PMR (DMSO-d₆) δ :

5 10.70 (s, 1H), 10.11 (s, 1H), 9.99 (s, 1H), 9.90 (s, 1H),
9.0 (b.s., 2H), 8.7 (b.s., 2H), 8.45 (d, J=1.7 Hz, 1H),
8.24 (s, 1H), 8.20 (t, J=5.7 Hz, 1H), 7.90 (m, 3H), 7.76
(dd, J=9.0 Hz and J=2.1 Hz, 1H), 7.30 (d, J=1.7 Hz, 1H),
7.22 (d, J=1.7 Hz, 1H), 7.16 (d, J=1.7 Hz, 1H), 7.10 (d,
10 J=1.7 Hz, 1H), 7.03 (d, J=1.7 Hz, 1H), 6.90 (d, J=1.7 Hz,
1H), 6.82 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.77 (s,
3H), 3.6-3.9 (m, 8H), 3.46 (m, 2H), 2.60 (m, 2H);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-

15 chloroethyl)aminobenzene-1-carboxamido]benzofuran-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine

hydrochloride;

FAB-MS: m/z 855, (8, [M+H]⁺)

20 U.V. (EtOH 95%) $\lambda_{\text{max}} = 313$, $\epsilon = 63866$

PMR (DMSO-d₆) δ :

10.72 (s, 1H), 10.08 (s, 1H), 10.04 (s, 1H), 9.93 (s, 1H),
8.90 (b.s., 4H), 8.28 (d, J=2.6 Hz, 1H), 8.23 (t, J=5.6 Hz,
1H), 7.91 (m, 2H), 7.76 (dd, J=9.0 Hz and J=2.1 Hz, 1H),
25 7.68 (s, 1H), 7.65 (d, J=9.0 Hz, 1H), 7.34 (d, J=1.7 Hz,
1H), 7.26 (d, J=1.7 Hz, 1H), 7.19 (d, J=1.7 Hz, 1H), 7.16
(d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H), 6.95 (d, J=1.7
Hz, 1H), 6.86 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.81 (s,
3H), 3.7-3.9 (m, 8H), 3.50 (m, 2H), 2.62 (m, 2H);

30

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-

chloroethyl)aminobenzene-1-carboxamido]benzimidazole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine
hydrochloride;

5 FAB-MS: m/z 856, (100, [M+H]⁺)

PMR (DMSO-d₆) δ :

11.05 (s, 1H), 10.06 (s, 1H), 10.04 (s, 1H), 9.92 (s, 1H),
8.96 (b.s., 2H), 8.60 (b.s., 2H), 8.28 (m, 1H), 8.22 (t,
J=5.9 Hz, 1H), 7.90 (m, 2H), 7.64 (m, 2H), 7.39 (d, J=1.7
10 Hz, 1H), 7.25 (d, J=1.7 Hz, 1H), 7.20 (d, J=1.7 Hz, 1H),
7.18 (d, J=1.7 Hz, 1H), 7.07 (d, J=1.7 Hz, 1H), 6.95 (d,
J=1.7 Hz, 1H), 6.85 (m, 2H), 3.6-3.9 (m, 17H), 3.50 (m,
2H), 3.60 (m, 2H);

15 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N,N-
bis(2-chloroethyl)aminobenzene-1-
carboxamido]benzimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;

20 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]benzothiazole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine
hydrochloride;

25 3-[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
bromoethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;

30 3-[1-methyl-4[1-methyl-4[1-methyl-5-[4-N,N-bis(2-
bromoethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;

3-[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-bromoethyl)aminobenzene-1-carboxamido]benzoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

5 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-bromoethyl)aminobenzene-1-carboxamido]indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

10 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N,N-bis(2-bromoethyl)aminobenzene-1-carboxamido]indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

15 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-bromoethyl)aminobenzene-1-carboxamido]benzoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

20 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N-ethyl-N(2-chloroethyl)aminobenzene-1-carboxamido]indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

25 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N-ethyl-N(2-chloroethyl)aminobenzene-1-carboxamido]benzoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

30 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N-ethyl-N(2-chloroethyl)aminobenzene-1-carboxamido]indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-

carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;
3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N-ethyl-
N(2-chloroethyl)aminobenzene-1-carboxamido]benzimidazole-
5 2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride.

Example 4

10

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]benzothiophene-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine
15 hydrochloride

*Step I: The intermediate 3-[1-methyl-4-[1-methyl-4[1-
methyl-4[4-nitrobenzothiophene-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
20 carboxamido]pyrrole-2-carboxamido]propionamidine
dihydrochloride*

To a solution of 156 mg of 4-nitrobenzothiophene-2-carboxylic acid (prepared as reported in *Synth.Commun.* 21, 959 (1991)) in 10 ml of benzene, 0.5 ml of thionyl chloride
25 were added. The mixture was refluxed for two hours, the solvent evaporated under vacuum, the crude solid residue dissolved in 15 ml of dioxane and added portionwise to a solution of 200 mg of N-deformyldistamycin A dihydrochloride (prepared as reported in *J.Med.Chem.* 32, 774-778 (1989)), 95 mg of sodium bicarbonate in 10 ml of water.

The mixture was stirred for one hour and then added of 2N

hydrochloric acid up to pH=4. The solvent was evaporated in vacuo and the residue purified by flash chromatography with a methylene chloride/methanol mixture to yield 220 mg of the title compound as a solid.

5

By analogous procedure and using the opportune starting materials the following products can be obtained:

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-nitrobenzofurane-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-

10 carboxamido]pyrrole-2-carboxamido]propionamidine dihydrochloride;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-nitroindole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine

15 dihydrochloride;

3-[1-methyl-4[1-methyl-4[4-nitroindole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine dihydrochloride;

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-4-nitroindole-2-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine dihydrochloride;

3-[1-methyl-4[1-methyl-4[1-methyl-4-nitroindole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-

25 carboxamido]propionamidine dihydrochloride;

3-[1-methyl-4[1-methyl-4[1-methyl-4[4-nitrobenzoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine dihydrochloride;

30 3-[1-methyl-4[1-methyl-4[4-nitrobenzoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine dihydrochloride;

- 40 -

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-4-
nitrobenzimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine dihydrochloride;

5 3-[1-methyl-4[1-methyl-4[1-methyl-4[4-nitrobenzothiazole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine
dihydrochloride.

10 **Step II: The title compound**

The derivative (220 mg) obtained from Step I was dissolved in 10 ml of DMF and reduced over Pd catalyst (10% on charcoal) under reduced pressure (50 psi) in a Parr apparatus. The solution obtained after filtration of the catalyst was evaporated in vacuo and the solid residue dissolved in 5 ml of dry DMF, cooled to 5°C and added with 0.055 ml of N,N'-diisopropylethylamine. After 10 min, 100 mg of 4-N,N-bis(2-chloroethyl)aminobenzoic acid (prepared as reported in Example 1, Step I) and 123 mg of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide were added. The solution was stirred for 12 hours at room temperature, then 2N hydrochloric acid was added up to pH=4. The solvent was evaporated and the crude residue purified by flash chromatography (methylene chloride/methanol : 8/2) to give 200 mg of the title compound as a yellow solid.

FAB-MS: m/z 871, (20, [M+H]⁺)

U.V. (EtOH 95%) $\lambda_{\text{max}} = 313.8$, $\epsilon = 48830$

PMR (DMSO-d₆) δ :

10.70 (s, 1H), 10.11 (s, 1H), 9.99 (s, 1H), 9.90 (s, 1H),
30 9.0 (b.s., 2H), 8.7 (b.s., 2H), 8.45 (d, J=1.7 Hz, 1H),
8.24 (s, 1H), 8.20 (t, J=5.7 Hz, 1H), 7.90 (m, 3H), 7.76
(dd, J=9.0 Hz and J=2.1 Hz, 1H), 7.30 (d, J=1.7 Hz, 1H),

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7.22 (d, $J=1.7$ Hz, 1H), 7.16 (d, $J=1.7$ Hz, 1H), 7.10 (d, $J=1.7$ Hz, 1H), 7.03 (d, $J=1.7$ Hz, 1H), 6.90 (d, $J=1.7$ Hz, 1H), 6.82 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.6-3.9 (m, 8H), 3.46 (m, 2H), 2.60 (m, 2H).

5

By analogous procedure and using the opportune starting materials the following products can be obtained:

3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -bromoacrylamido)indole-2-carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

FAB-MS: m/z 269, (10, $[M+H]^+$)

U.V. (EtOH 95%) $\lambda_{max} = 310$, $\epsilon = 35011$

PMR (DMSO- d_6) δ :

10.39 (s, 1H), 10.18 (s, 1H), 9.93 (s, 1H), 8.92 (b.s., 2H), 8.54 (b.s., 2H), 8.19 (t, $J=5.7$ Hz, 1H), 8.01 (d, $J=1.5$ Hz, 1H), 7.50 (d, $J=9.0$ Hz, 1H), 7.42 (dd, $J=9.0$ Hz and $J=1.5$ Hz, 1H), 7.29 (d, $J=1.8$ Hz, 1H), 7.16 (s, 1H), 7.15 (d, $J=1.8$ Hz, 1H) 7.06 (d, $J=1.8$ Hz, 1H), 6.92 (d, $J=1.8$ Hz, 1H), 6.72 (d, $J=3.1$ Hz, 1H), 6.25 (d, $J=3.1$ Hz, 1H), 3.97 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.44 (m, 2H), 2.60 (m, 2H);

3-[1-methyl-4[1-methyl-4[1-methyl-4[5(α -bromoacrylamido)benzofurane-2-carboxamido]pyrrole-2-

25 carboxamido]pyrrole-2-carboxamido]propionamidine hydrochloride;

FAB-MS: m/z 746, (25, $[M+H]^+$)

U.V. (EtOH 95%) $\lambda_{max} = 315.4$, $\epsilon = 42622$

PMR (DMSO- d_6) δ :

30 10.69 (s, 1H), 10.39 (s, 1H), 10.00 (s, 1H), 9.90 (s, 1H), 8.92 (b.s., 2H), 8.52 (b.s., 2H), 8.2 (m, 2H), 7.66 (m,

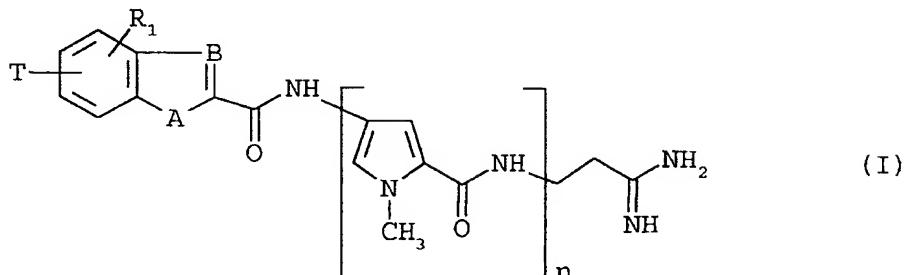
- 42 -

3H), 7.32 (d, J=1.8 Hz, 1H), 7.24 (d, J=1.8 Hz, 1H), 7.17
(d, J=1.8 Hz, 1H), 7.15 (d, J=1.8 Hz, 1H) 7.07 (d, J=1.8
Hz, 1H), 6.96 (d, J=1.8 Hz, 1H), 6.77 (d, J=3.1 Hz, 1H),
6.31 (d, J=3.1 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80
5 (s, 3H), 3.51 (m, 2H), 2.60 (m, 2H);

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α-
chloroacrylamido)benzoimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
10 carboxamido]propionamidine hydrochloride;
3- [1-methyl-4 [1-methyl-4 [5- [4-N,N-bis (2-
chloroethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;
15 3- [1-methyl-4 [1-methyl-4 [5- [4-N,N-bis (2-
chloroethyl)aminobenzene-1-carboxamido]benzoimidazole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine hydrochloride;
3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5- [4-N-ethyl-N (2-
20 chloroethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine
hydrochloride;
3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5- [4-N-ethyl-N (2-
25 chloroethyl)aminobenzene-1-carboxamido]benzoimidazole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine
hydrochloride.

CLAIMS

1. A compound which is a benzoheterocyclic distamycin derivative of formula:



5

wherein:

n is 2, 3 or 4;

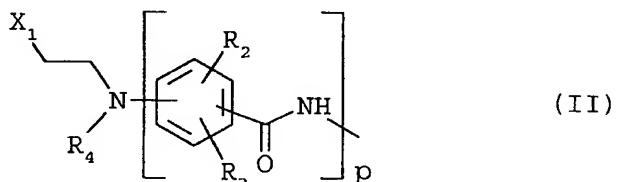
A is O, S or NR, wherein R is hydrogen or C₁-C₄ alkyl;

B is CH or N;

10 R₁ is hydrogen or C₁-C₄ alkyl;

T is selected from:

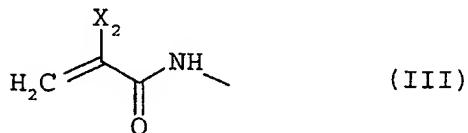
(i)



wherein:

15 p is zero or 1; R₂ and R₃ are selected, each independently, from: hydrogen, C₁-C₄ alkyl optionally substituted by one or more fluorine atoms, and C₁-C₄ alkoxy; R₄ is C₁-C₄ alkyl or C₁-C₃ haloalkyl; X₁ is a halogen atom; and

20 (ii)



wherein X₂ is a halogen atom;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein:

n is 2 or 3;

5 A is O, S, NH or NCH₃;

B is CH or N;

R₁ is hydrogen;

T is a group of formula (II) according to item (i), wherein

X₁ is chlorine or bromine; R₄ is ethyl, 2-chloroethyl or 2-

10 bromoethyl; R₂ and R₃ are, each independently, hydrogen or methyl; p is zero or 1; or

T is a group of formula (III) according to item (ii), wherein X₂ is bromine or chlorine.

15 3. A compound according to claim 1, selected from:

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5-N,N-bis (2-chloroethyl)aminoindole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

20 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [1-methyl-5-N,N-bis (2-chloroethyl)aminoindole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5-N,N-bis (2-

25 chloroethyl)aminobenzofurane-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5-N,N-bis (2-chloroethyl)aminobenzimidazole-2-carboxamido]pyrrole-2-

30 carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [1-methyl-5-N,N-bis (2-

chloroethyl)aminobenzimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5-N,N-bis (2-
5 chloroethyl)aminobenzothiophene-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5-N,N-bis (2-
chloroethyl)aminobenzothiazole-2-carboxamido]pyrrole-2-
10 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5-N,N-bis (2-bromoethyl)
aminoindole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-
2-carboxamido]pyrrole-2-carboxamido]propionamidine;

15 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -bromoacrylamido)
indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -bromoacrylamido)
indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-
20 carboxamido]pyrrole-2-carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [1-methyl-5 (α -
bromoacrylamido)indole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

25 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
bromoacrylamido)benzofurane-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
30 bromoacrylamido)benzothiophene-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-

carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
bromoacrylamido)benzothiazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
5 carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
bromoacrylamido)benzimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

10 3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [1-methyl-5 (α -
bromoacrylamido)benzimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
15 chloroacrylamido)indole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [1-methyl-5 (α -
chloroacrylamido)indole-2-carboxamido]pyrrole-2-
20 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [1-methyl-4 [5 (α -
chloroacrylamido)benzimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
25 carboxamido]propionamidine;

3- [1-methyl-4 [1-methyl-4 [5- [4-N, N-bis (2-
chloroethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

30 3- [1-methyl-4 [1-methyl-4 [5- [4-N, N-bis (2-
chloroethyl)aminobenzene-1-carboxamido]benzimidazole-2-

carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]indole-2-
5 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N,N-
bis(2-chloroethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
10 carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]benzothiophene-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

15 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]benzofurane-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
20 chloroethyl)aminobenzene-1-carboxamido]benzoimidazole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N,N-
bis(2-chloroethyl)aminobenzene-1-
25 carboxamido]benzoimidazole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
chloroethyl)aminobenzene-1-carboxamido]benzothiazole-2-
30 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-

bromoethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-5-[4-N,N-bis(2-
5 bromoethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
bromoethyl)aminobenzene-1-carboxamido]benzimidazole-2-
10 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
bromoethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
15 carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N,N-bis(2-
bromoethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

20 3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N,N-bis(2-
bromoethyl)aminobenzene-1-carboxamido]benzimidazole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N-ethyl-N(2-
25 chloroethyl)aminobenzene-1-carboxamido]indole-2-
carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

3-[1-methyl-4[1-methyl-4[1-methyl-4[5-[4-N-ethyl-N(2-
chloroethyl)aminobenzene-1-carboxamido]benzimidazole-2-
30 carboxamido]pyrrole-2-carboxamido]pyrrole-2-
carboxamido]pyrrole-2-carboxamido]propionamidine;

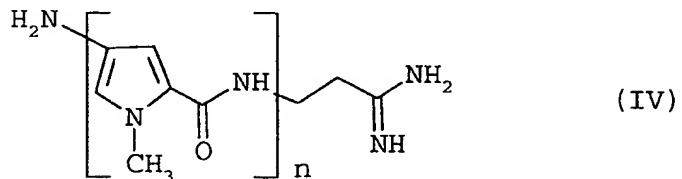
3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[4-N-ethyl-

N(2-chloroethyl)aminobenzene-1-carboxamido]indole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
 3-[1-methyl-4[1-methyl-4[1-methyl-4[1-methyl-5-[-4-N-ethyl-
 5 N(2-chloroethyl)aminobenzene-1-carboxamido]benzoimidazole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine;
 and the pharmaceutically acceptable salts thereof.

10

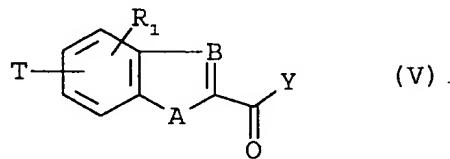
4. A process for producing a compound as defined in claim 1, which process comprises:

(1) (a) reacting a compound of formula:



15

wherein n is 2, 3 or 4, with a compound of formula:



wherein:

A is O, S or NR, wherein R is hydrogen or C₁-C₄ alkyl;

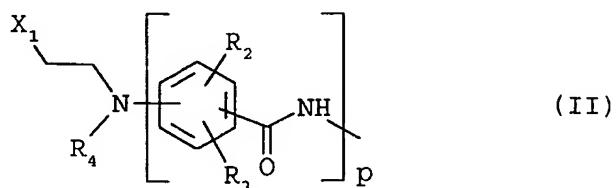
B is CH or N;

20

R₁ is hydrogen or C₁-C₄ alkyl;

T is selected from:

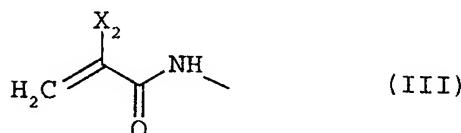
(i)



-50-

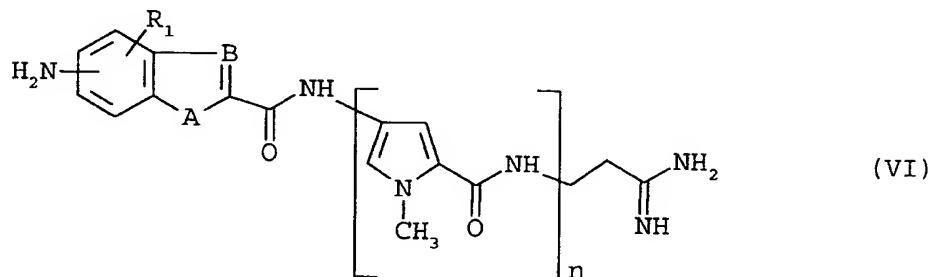
wherein:

5 p is zero or 1; R₂ and R₃ are selected, each independently, from: hydrogen, C₁-C₄ alkyl optionally substituted by one or more fluorine atoms, and C₁-C₄ alkoxy; R₄ is C₁-C₄ alkyl or C₁-C₃ haloalkyl; X₁ is a halogen atom; and
 (iii)

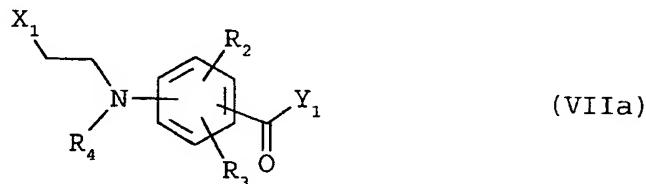


10 wherein X₂ is a halogen atom;
 Y is hydroxy or a leaving group;
 to obtain a compound of formula (I) as defined above;
 or:

(b) reacting a compound of formula:



15 wherein n, A, B, and R₁ are defined as above,
 with a compound of formula:



wherein X₁, R₂, R₃, and R₄ are defined as above, and Y₁ is hydroxy or a leaving group;
 20 or with a compound of formula:

- 51 -

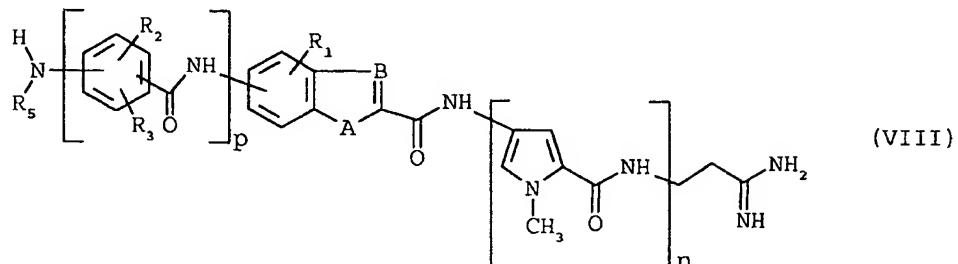


wherein X_2 is as defined above, and Y_2 is hydroxy or a leaving group;

5 to obtain a compound of formula (I) as defined above, wherein T is a group of formula (II) according to item (i) with p equal to 1, or a group of formula (III) according to item (ii);

or:

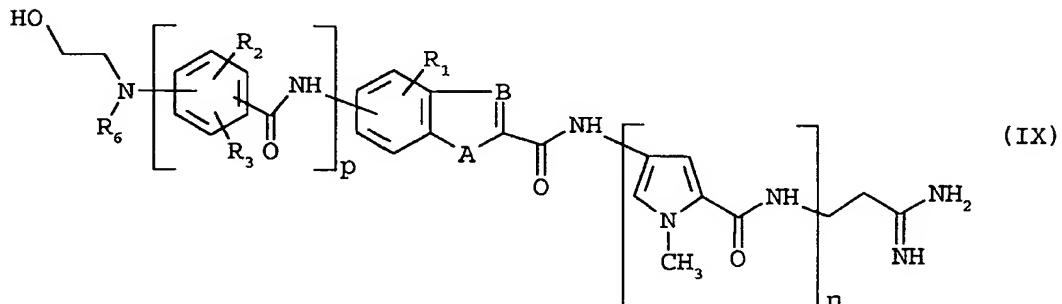
(c) reacting a compound of formula:



10

wherein p , n , A , B , R_1 , R_2 , and R_3 are defined as above, and R_5 is hydrogen or C_1-C_4 alkyl,

with ethylene oxide, so obtaining a compound of formula:



15

wherein p , n , A , B , R_1 , R_2 , and R_3 are defined as above, and R_6 is equal to R_5 when R_5 is C_1-C_4 alkyl, or R_6 is equal to $-CH_2CH_2-OH$ when R_5 is hydrogen;

and then reacting the compound of formula (IX) with a 20 halogenating agent, to obtain a compound of formula (I)

-52-

as defined above, wherein T is a group of formula (II) according to item (i) with p equal to zero or 1; and

5 (2) if necessary, converting the so obtained compound of formula (I) into a pharmaceutically acceptable salt thereof.

10 5. A compound as defined in any one of claims 1 to 3 for use in a method of treating the human or animal body by therapy.

6. A compound as claimed in claim 5 for use as an antineoplastic agent.

15 7. A compound as claimed in claim 5 for use as an antiviral agent.

20 8. Use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for use in the treatment of cancer.

9. Use of a compound as defined in any one of claims 1 to 3 in the manufacture of a medicament for use in the treatment of a viral infection.

25

10. A pharmaceutical composition which comprises an effective amount of a compound as defined in any one of claims 1 to 3 as an active principle, in association with one or more pharmaceutically acceptable carriers and/or diluents.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/05986

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D403/14 A61K31/40 C07D407/14 A61K31/415 C07D409/14
C07D417/14 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 246 868 A (FARMITALIA CARLO ERBA S.P.A.) 25 November 1987 cited in the application see claims 1-4,6-9 ---	1-10
Y	ARCAMONE F.M. ET AL.: "SYNTHESIS, DNA-BINDING PROPERTIES, AND ANTITUMOR ACTIVITY OF NOVEL DISTAMYCIN DERIVATIVES" JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 4, 1989, pages 774-778, XP000608784 see the whole document ---	1-10
Y	WO 93 13739 A (MENARINI, A., INDUSTRIE FARMACEUTICHE RIUNITE S.R.L.) 22 July 1993 see claims 1-3,23-28 ---	1-10 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

1

Date of the actual completion of the international search 6 March 1998	Date of mailing of the international search report 27.03.98
---	--

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer
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Hartrampf, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/05986

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 20463 A (A. MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L.) 15 September 1994 see claims 1-3,10-15 ---	1-10
Y	D'ALESSIO R. ET AL.: "Structure-activity relationship of novel distamycin A derivatives: Synthesis and antitumor activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , vol. 4, no. 12, December 1994, pages 1467-1472, XP000671766 see the whole document ---	1-10
Y	WO 96 05196 A (PHARMACIA S.P.A.) 22 February 1996 see claims 1-3,5-9 ---	1-10
P,Y	WO 97 03957 A (PHARMACIA & UPJOHN S.P.A.) 6 February 1997 see the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. national Application No

PCT/EP 97/05986

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 246868 A	25-11-87	AU 597659 B		07-06-90
		AU 7316387 A		26-11-87
		BG 60531 B		28-07-95
		CA 1314551 A		16-03-93
		CS 9104137 A		16-09-92
		DE 3781716 A		22-10-92
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